Whole genome sequencing used to help inform cancer therapy

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Whole genome sequencing — spelling out a person's entire DNA genetic code — has moved one step closer to being a medical option for direct patient care.

Physicians and researchers at Mayo Clinic in Arizona and the Translational Genomics Research Institute (TGen) successfully completed sequencing both a single patients normal and cancer cells – a tour de force of more than 6 billion DNA chemical bases.

While the whole genomes of several individuals or their cancers have been sequenced in recent years, this is believed to be among the first successful application of whole genome sequencing performed in support of the medical care of a specific cancer patient.

A male patient with pancreatic cancer was the first patient at Mayo Clinic to have whole genome sequencing performed on both his tumor and non-cancerous cells as part of a clinical research project. By comparing the tumor DNA to the patient's normal DNA, researchers found genetic changes (mutations) that were important in helping inform doctors about how best to plan the patient's next treatment. This was a case of using a definable genetic change that could be linked to specific treatment, something believed to be a glimpse into the almost certain future of individualizing cancer care.

Mayo Clinic administered all the clinical aspects of the research. TGen performed the genetic sequencing.

While the Mayo-TGen sequencing was done as part of ongoing research, it signals a major step toward implementation of whole genome sequencing to support clinic treatment options.

"This is a demonstration of the clinical utility of whole genome sequencing," said Keith Stewart, M.B., Dean of Research at Mayo Clinic. "As we do more and more of this, we will move closer and closer to personalized genetic medicine, which means using genetic information to minimize or prevent disease."

Details of this research, its results and implications for the future, will be included in an upcoming scientific paper.

In 2003, after 13 years and nearly $2.7 billion, the government-funded international Human Genome Project deciphered the first entire human genome sequence. Continuing technological advances now allow scientists to evaluate the entire human genome at a fraction of the time and cost.

"No one thought that this would be possible this soon, and the key now is to combine all medical and scientific information together," said Mitesh J. Borad, M.D., Assistant Professor of Medicine and oncology specialist at Mayo Clinic. "However, we are still very early in the process. A lot of questions will come out of this. But in the long run, this will only help."

Other sequencing techniques — such as genome-wide association studies — are less expensive tests, but examine only selected portions of DNA. Whole genome sequencing (WGS) looks at the entire genome, giving scientists the most comprehensive view of the potential genetic origins of disease.

" Increasingly we will use information from an individuals DNA sequence to expand from today's attempts to define disease risk to actual

disease management," said Jeffrey Trent, Ph.D., President and Research Director at TGen and the former Scientific Director of the federal government's National Human Genome Research Institute. "We recognize our lack of complete knowledge of many of the genetic changes we observe, and how exactly they will align with drugs for treatment. However, the use of new compounds for some leukemias and gastrointestinal tumors with defined genetic alterations is the prototype example of a genetic change matched to a targeted therapy providing profound clinical benefit. Our study is one of a handful now underway that is attempting to identify and then match a gene alteration to a targeted agents."

Performing genomic sequencing on cancerous tumors may provide clinicians with information to treat cancer more precisely, especially for patients who are resistant to traditional treatments. Cancer is a disease often rooted in genetic mutations and can change a person's DNA. Essentially, WGS distills all the molecular ingredients that make up a person's genetics so physicians can pinpoint the root cause of a disease. The knowledge gained from this research should allow clinicians to design treatments to address many specific diseases.

"Every step we take in research gets us closer to making this routine for cancer patients," said Rafael Fonseca, M.D., Deputy Director, Mayo Clinic Cancer Center in Arizona. "If we look in the not too distant future, this is a possibility for every cancer patient."

At this point, start-up costs for WGS are still significant. Genetic sequencing of tumors requires immense technological and human resources. Once processes are developed and regularly implemented, the long-term costs of sequencing are expected to further drop.

"Whole genome sequencing allows us to dig deeper into the genome than ever before by providing more information and increasing our

probability of identifying an 'Achilles heel' not previously recognized by more conventional approaches," said John Carpten, Ph.D., Director of TGen's Integrated Cancer Genomics Division. "The long-term hope is that doctors will leverage this information to inform decisions about patient care in cancer, and beyond."

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